Glycemia and Its Relationship to Outcomes in the Metformin in Gestational Diabetes Trial

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OBJECTIVE — To determine how glucose control in women with GDM treated with metformin and/or insulin influenced pregnancy outcomes.

RESEARCH DESIGN AND METHODS — Women randomly assigned to metformin or insulin treatment in the Metformin in Gestational Diabetes (MiG) trial had baseline glucose tolerance test (OGTT) results and A1C documented, together with all capillary glucose measurements during treatment. In the 724 women who had glucose data for analysis, tertiles of baseline glucose values and A1C and of mean capillary glucose values during treatment were calculated. The relationships between maternal factors, glucose values, and outcomes (including a composite of neonatal complications, preeclampsia, and large-for-gestational-age [LGA] and small-for-gestational-age infants) were examined with bivariable and multivariate models.

RESULTS — Baseline OGTT did not predict outcomes, but A1C predicted LGA infants ($P = 0.003$). During treatment, fasting capillary glucose predicted neonatal complications ($P < 0.001$) and postprandial glucose predicted preeclampsia ($P = 0.016$) and LGA infants ($P = 0.001$). Obesity did not influence outcomes, and there was no interaction between glycemic control, randomized treatment, or maternal BMI in predicting outcomes. The lowest risk of complications was seen when fasting capillary glucose was <4.9 mmol/l (mean ± SD 4.6 ± 0.3 mmol/l) compared with 4.9–5.3 mmol/l or higher and when 2-h postprandial glucose was 5.9–6.4 mmol/l (6.2 ± 0.2 mmol/l) or lower.

CONCLUSIONS — Glucose control in women with gestational diabetes mellitus treated with metformin and/or insulin is strongly related to outcomes. Obesity is not related to outcomes in this group. Targets for fasting and postprandial capillary glucose may need to be lower than currently recommended.

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Although treatment of gestational diabetes mellitus (GDM) has been shown to improve perinatal outcomes (1,2), there is lack of consensus about ideal glucose targets and how other factors, such as fetal abdominal circumference, should influence these targets (3,4). The Fifth International Workshop-Conference on Gestational Diabetes endorsed targets of capillary fasting glucose <5.3 mmol/l, 1-h postprandial <7.8 mmol/l, and/or 2-h postprandial <6.7 mmol/l until further data addressing optimal goals become available (5). Improved pregnancy outcomes have been reported in women achieving these targets compared with those in women who did not (6); the latter group had higher baseline mean BMI and A1C, which may have influenced outcomes. Obesity has been reported as an independent factor influencing outcome in women with GDM treated with diet but not in those treated with insulin (7,8).

Published studies have compared women who aim for or achieve predetermined glucose targets with those who do not: it is not clear whether such aims are optimal and whether glycemia influences different outcomes equally. Several studies suggested that treatment intensity can be usefully stratified according to fetal abdominal circumference measured by ultrasound (3): intensive treatment of women carrying fetuses with an abdominal circumference above the 70–75th percentile lowered the frequency of large-for-gestational-age (LGA) infants without increasing rates of small-for-gestational-age (SGA) infants. However, lowering of mean maternal glucose to <4.8 mmol/l is associated with increased frequency of SGA infants (9).

Data showing relationships between different fasting and postprandial glucose values and a range of outcomes would assist clinicians in setting target ranges for "optimal glucose control" more objectively. In the Metformin in Gestational Diabetes (MiG) trial, women with GDM, who had one or more home capillary blood glucose measures ≥5.5 mmol/l fasting or ≥6.7 mmol/l 2-h postprandial after lifestyle intervention, were randomly assigned to either insulin or metformin treatment (10). The primary objective of the trial was to compare metformin with insulin treatment, but prespecified secondary objectives were to determine the impact of glycemia on outcomes and to determine whether treatment with metformin or insulin was more effective at different levels of glycemia. Baseline glycemia measures and capillary glucose measures throughout treatment were recorded in the trial database. The specific aims of the present analysis were *1*) to determine how glucose control influenced trial outcomes, including the primary outcome (a composite of neonatal complications), maternal preeclampsia, and rates of LGA and SGA infants; *2*) to identify additional baseline factors influencing outcomes, including baseline glycemia and obesity; and *3*) to examine any differences between treatment arms at different levels of glycemia.

RESEARCH DESIGN AND METHODS

The MiG trial was a prospective, randomized, multicenter trial comparing metformin with insulin treatment in women with GDM. The methodology and outcomes have been published previously (10). The mean gestation at recruitment was 30 ± 3 weeks. All women gave written informed consent. The trial was approved by ethics committees at each participating site.

Assessment of glycemia

Baseline glycemia measures included the diagnostic 75-g oral glucose tolerance test (OGTT) results and A1C at random assignment to treatment with insulin or metformin. Treatment glycemia measures included capillary glucose measurements that were documented four times daily: fasting and 2 h from the start of each meal. Medisense (now Optium) meters (Abbott Diabetes Care, Alameda, CA) and occasional Accu-Chek Advantage meters (Roche Diagnostics, Mannheim, Germany) were used, and the stored results were downloaded. Relevant results were transcribed into the trial database from the day after medication was started until delivery. Of 733 women who had data collected, 7 women did not have fasting glucose, 8 did not have postprandial glucose, and 9 did not have any glucose recordings documented, leaving 724 women for assessment. The median number (interquartile range) of capillary glucose values documented for each woman included 46 (34–60) fasting and 115 (83–161) postprandial measures. The means of fasting and postprandial glucose measures were calculated separately for each patient.

Outcomes and definitions

Several prespecified outcomes from the trial were selected to examine the impact of glycemia measures: the primary outcome composite (neonatal complications), preeclampsia, and rates of LGA (customized birth weight >90th percentile) and SGA (customized birth weight <10th percentile) infants. The primary outcome composite included one or more of the following neonatal complications: recurrent hypoglycemia (two or more blood glucose measurements <2.6 mmol/l), respiratory distress (need for ≥4 h of respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive-pressure ventilation during first 24 h), need for phototherapy, birth trauma,

5-min Apgar score <7, and preterm birth (<37 weeks of gestation). The birth weight percentile was calculated using customized calculators (http://www.gestation.net), which adjust for sex and gestational age of the infant as well as for maternal height, weight in early pregnancy, ethnic group, and parity (11). In this calculator, birth weight is adjusted if a woman's BMI is between 20 and 30 kg/m^2 but not further adjusted for BMI above this range; European, Maori, Chinese, Indian, and other specific Asian and Pacific Island ethnicities can be selected. In the MiG database, the specific Pacific Island ethnicity was not documented, so Samoan ethnicity was used to represent this group in the calculations. Of note, customized charts applied to a general nondiabetic obstetric population with ethnicities similar to those of the MiG population report rates of SGA infants between 12.1 and 12.8% and of LGA infants between 8.4 and 8.8% (http://www.adhb.govt.nz/nwhealthinfo).

Statistical analysis

Mean capillary glucose values were calculated from the daily records. They are shown as mean fasting, mean postprandial, and/or overall mean glucose (mean fasting plus mean postprandial divided by 2). Fasting, postprandial, and overall mean glucose measures and their relationship to outcomes were explored using continuous measures and categorized quartile and tertile groupings; all methods yielded similar relationships. Tertile groups were chosen for this report because, with larger numbers in each group, they provided a simple demonstration of relationships between glucose levels and outcomes. A bivariable analysis of baseline characteristics was performed to explore associations with outcomes. Interactions with glycemic control, both of randomized treatment (metformin or insulin) and of obesity, were explored using the Breslow-Day test through stratified analysis and logistic regression analysis. Multivariable binary logistic regression was performed to identify independent risk factors associated with both the primary composite outcome measure and preeclampsia. For the customized birth weight percentiles, multinomial logistic regression was used, given that the outcome measure was categorized into three groups: appropriate-for-gestational-age, SGA, and LGA infants. In these analyses, the backwards elimination method was used. Specifically, any potential risk factors identified through bivariable anal-

ysis and stratified analysis ($P < 0.25$), as well as others considered potentially relevant for clinical reasons or from the literature, were included in the initial models; variables were then eliminated stepwise from the models if their contributions were not significant, until all variables retained were significantly associated with the outcome measure. Two multivariable analysis models were examined. In the first, the glycemic measures included the baseline OGTT results, A1C values, and mean fasting, postprandial, and overall capillary glucose concentrations in addition to other potential baseline risk factors (total available $n = 582$ for this model for the primary composite outcome). In the second model, the baseline glycemia measures were excluded, giving a total $n = 724$ for the analysis of primary composite measures. Interpretation of the results relating to risk factors for SGA and LGA infants took into account the fact that the "customized" classification of SGA and LGA infants had already been adjusted for infant sex, gestation, maternal ethnicity, parity, and BMI between 20 and 30 kg/m^2.

Maternal weight at the earliest booking was missing in 147 women, so these data were imputed using a regression method. Specifically, the weight was first imputed using a formula based on the postpregnancy weight. If this variable was missing, then a formula based on the randomization weight was used instead. The imputed mean of weight at the earliest booking was 85.98 kg, very close to the mean of 85.25 kg before imputation, suggesting that the imputation is robust.

All analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC), using $\alpha = 0.05$ to determine significance.

RESULTS

Table 1 shows tertiles of baseline glycemia measures and capillary glucose levels during treatment. Supplementary Table 1A (available at http://care.diabetesjournals.org/cgi/content/full/dc09-1407/DC1) shows baseline characteristics of the women according to tertiles of capillary glucose during treatment.

The relationships between tertiles of mean fasting, postprandial, and overall capillary glucose during treatment and outcomes are shown in Table 2. Examining the components of the primary outcome composite, we note that the frequencies of recurrent neonatal hypoglycemia and preterm birth increased across tertiles of control, and there was a

Table 1—*Baseline and treatment glycemia tertiles*

	Tertile 1 upper limit	Tertile 1	Tertile 2 limits	Tertile 2	Tertile 3 lower limit	Tertile 3
Baseline measures						
OGTT fasting glucose (mmol/l)	5.2	4.7 ± 0.3	5.2–5.8	5.5 ± 0.2	5.8	6.8 ± 1.1
OGTT 2-h glucose (mmol/l)	8.8	7.5 ± 1.0	8.8–9.9	9.4 ± 0.3	9.9	11.6 ± 1.8
A1C (%)	5.4	5.1 ± 0.3	5.4–5.8	5.7 ± 0.1	5.8	6.5 ± 0.6
Treatment measures						
Fasting capillary glucose (mmol/l)	4.9	4.6 ± 0.3	4.9–5.3	5.1 ± 0.1	5.3	5.9 ± 0.6
Postprandial capillary glucose (mmol/l)	5.9	5.6 ± 0.2	5.9–6.4	6.2 ± 0.2	6.4	7.2 ± 0.7
Mean capillary glucose (mmol/l)	5.4	5.2 ± 0.2	5.4–5.8	5.7 ± 0.1	5.8	6.5 ± 0.6

Data are tertile boundaries and mean ± SD glycemia measures within each tertile. Glucose and A1C were recorded to 1 decimal place.

trend to higher rates of respiratory distress and a need for phototherapy. Maternal preeclampsia and frequency of LGA infants also increased across tertiles of achieved glycemia. The frequency of SGA infants fell across the tertiles of fasting and mean glycemia but not across the postprandial tertiles. The frequency of SGA infants in the lowest fasting tertile was not increased compared with that of the background population.

The bivariable relationships between maternal baseline characteristics, glycemia measures, and outcomes are shown in Table 3. Baseline factors that were related to the primary outcome composite included maternal ethnicity, nulliparity, previous preeclampsia, and previous delivery of a baby weighing >4,000 g. Baseline glycemia measures were not related to the primary outcome composite, but mean capillary glucose measures on treatment were strongly related. Preeclampsia was associated with Polynesian ethnicity, chronic hypertension, previous hypertensive complications during pregnancy, and maternal weight gain from early pregnancy to recruitment. It was also associated with baseline A1C and all measures of glucose control on treatment. Additional factors (not all shown) that were not related to either the primary outcome composite or preeclampsia included gestation at recruitment (20–27 vs. 28–33 weeks), tertiary education level, smoking in pregnancy, past history of GDM, previous recurrent miscarriage/termination (three or more), and maternal first-degree family history of diabetes, hypertension, or preeclampsia.

In Table 3, the frequency of SGA infants was associated with Asian ethnicity and with the woman having a first-degree relative with diabetes. It was inversely related to maternal weight gain from early pregnancy to recruitment. Baseline glycemia measures were not predictive of SGA infants. During treatment, risk of SGA infants was lower in women in the highest tertile of capillary fasting glucose, but there was no relationship with postprandial glucose. The frequency of LGA infants was associated with Polynesian ethnicity, previous delivery of a baby weighing >4,000 g, maternal weight gain from early pregnancy to recruitment, and A1C at recruitment. The rate of LGA infants was increased in women whose capillary glucose during treatment was in the highest tertile. Other factors (not shown) that did not relate to SGA or LGA infants included chronic hypertension, gestation at recruitment, smoking in pregnancy, tertiary education, previous history of recurrent miscarriages/terminations, GDM or hypertensive complications, and a family history of preeclampsia. The Breslow-Day test and logistic regression analysis showed no interactions of glycemic control with randomized treatment or with maternal BMI in predicting the primary

Table 2—*Outcomes by fasting, postprandial tertiles, and overall mean glucose tertiles*

	Fasting tertiles				Postprandial tertiles				Mean glucose tertiles			
	1	2	3	*P**	1	2	3	*P**	1	2	3	*P**
Primary outcome components	22.9	32.5	39.6	<0.001	25.6	29.4	40.3	<0.001	23.0	31.1	41.4	<0.001
Recurrent glucose <2.6 mmol/l	10.4	18.3	21.3	0.002	13.0	17.7	19.3	0.07	11.7	15.3	23.2	<0.001
Respiratory distress	2.9	2.9	5.4	0.15	2.5	1.6	7.1	0.01	2.5	3.2	5.5	0.09
Phototherapy	5.4	8.1	10.8	0.03	7.1	6.9	10.5	0.18	5.4	9.7	9.3	0.13
Birth trauma	4.2	4.1	5.0	0.66	3.8	3.2	6.3	0.18	5.0	2.4	5.9	0.64
Apgar score <7 at 5 min	0.4	0	0.8	0.48	0	0	1.3	0.03	0	0	1.3	0.03
Prematurity: <37 weeks gestation	5.8	10.2	13.3	0.006	5.5	9.3	14.7	<0.001	5.9	10.5	13.1	0.008
Maternal preeclampsia	4.2	4.9	9.6	0.01	3.4	4.4	10.9	<0.001	3.4	5.2	10.1	0.002
Birth weight†				<0.001‡				<0.001‡				<0.001‡
<10th (customized)	13.8	11.4	6.7	0.01	11.8	10.5	9.7	0.46	13.8	9.7	8.4	0.06
>90th (customized)	12.1	11.4	24.6	<0.001	10.1	12.9	24.8	<0.001	10.5	13.3	24.1	<0.001
<2,500 g	5.0	6.5	5.0	1.0	2.9	6.5	7.1	0.045	4.6	6.5	5.5	0.672
>4,000 g	8.3	10.2	19.6	<0.001	6.7	13.3	17.7	<0.001	6.7	12.9	18.1	<0.001

Data are frequency of outcome (%). *Cochrane-Armitage trend test. †Customized charts in general obstetric population with ethnicities similar to those of the MiG population reported rates of SGA infants of 12.1–12.8% and of LGA infants of 8.4–8.8% (http://www.adhb.govt.nz/nwhealthinfo). ‡χ^2 test of three levels of customized birth weight.

Table 3—Bivariable analysis: baseline characteristics, glucose measures at baseline and on treatment, and their relationships to outcomes, including the primary outcome (for a composite of neonatal outcomes, see text), preeclampsia, and customized SGA and LGA

			Primary outcome			Preeclampsia			Customized SGA and LGA				
	n	%	OR (95% CI)	P	%	OR (95% CI)	P	SGA (%)	OR (95% CI)*	LGA (%)	OR (95% CI)*	P
Baseline characteristics												
Ethnicity												
European Caucasian/mixed	373	34.6	1.00	0.03	5.1	1.00	0.004	8.0	1.00	15.6	1.00	0.001
Polynesian	156	35.9	1.06 (0.72–1.57)		12.2	2.59 (1.3–5.03)		9.0	1.26 (0.64–2.46)	23.1	1.67 (1.04–2.68)	
Asian/other	204	24.5	0.61 (0.42–0.90)		3.9	0.76 (0.3–1.77)		16.7	2.20 (1.29–3.73)	11.3	0.77 (0.46–1.30)	
BMI range												
<25 kg/m²	131	24.4	1.00	0.08	3.8	1.00	0.39	13.0	1.00	11.5	1.00	0.07
25–29 kg/m²	183	31.2	1.40 (0.84–2.32)		7.7	2.09 (0.7–5.95)		10.9	0.82 (0.41–1.65)	11.5	0.98 (0.48–1.99)	
≥30 kg/m²	419	34.8	1.65 (1.06–2.59)		6.4	1.74 (0.6–4.60)		9.8	0.80 (0.44–1.48)	19.3	1.80 (0.99–3.27)	
Adjusted BMI category*												
Normal	100	23.0	1.00	0.11	1.0	1.00	0.06	14.0	1.00	11.0	1.00	0.26
Overweight	210	32.9	1.64 (0.95–2.83)		9.1	9.85 (1.3–74.65)		11.4	0.82 (0.40–1.67)	13.8	1.26 (0.60–2.66)	
Obese	423	33.8	1.71 (1.03–2.84)		6.2	6.48 (0.87–48.36)		9.5	0.70 (0.36–1.35)	18.2	1.72 (0.87–3.39)	
Chronic hypertension												
No	675	31.3	1.00	0.12	5.5	1.00	0.004	10.2	1	16.4	1	0.28
Yes	58	41.4	1.55 (0.90–2.68)		15.5	3.17 (1.45–6.94)		15.5	1.5 (0.70–3.22)	10.3	0.62 (0.26–1.50)	
Nulliparity												
No	500	29.6	1.00	0.04	5.4	1.00	0.16	9.8	1.00	18.4	1.00	0.03
Yes	233	37.3	1.42 (1.02–1.97)		8.2	1.56 (0.85–2.86)		12.5	1.19 (0.73–1.94)	10.7	0.55 (0.34–0.88)	
Weight change (kg) from early pregnancy to recruitment	733		1.01 (0.98–1.04)	0.612		1.05 (1.01–1.10)	0.031		0.95 (0.90–0.99)		1.06 (1.02–1.09)	<0.001
Past obstetric history												
Preeclampsia												
No	445	28.5	1.00	0.04	4.3	1.00	0.007	9.9	1	18.0	1	0.10
Yes	55	38.2	1.55 (0.87–2.77)		14.6	3.82 (1.58–9.19)		9.1	0.96 (0.36–2.57)	21.8	1.27 (0.63–2.54)	
Nulliparity	233	37.3	1.49 (1.07–2.09)		8.2	1.99 (1.03–3.84)		12.3	1.18 (0.72–1.96)	10.7	0.56 (0.35–0.91)	
Gestational hypertension												
No	440	28.9	1.00	0.07	3.9	1.00	<0.001	10.2	1	17.7	1	0.06
Yes	60	35.0	1.33 (0.75–2.35)		16.7	4.98 (2.16–11.46)		6.7	0.67 (0.23–1.96)	23.3	1.36 (0.71–2.60)	
Nulliparity	233	37.3	1.47 (1.05–2.06)		8.2	2.21 (1.13–4.34)		12.5	1.14 (0.69–1.88)	10.7	0.57 (0.35–0.92)	
Previous baby >4,000 g												
No	338	32.3	1.00	0.02	4.4	1.00	0.17	11.8	1.00	12.1	1.00	<0.001
Yes	162	24.1	0.67 (0.44–1.02)		7.4	1.72 (0.79–3.77)		5.6	0.57 (0.27–1.21)	31.5	3.13 (1.96–5.02)	
Nulliparity	233	37.3	1.25 (0.88–1.78)		8.2	1.91 (0.95–3.85)		12.5	1.04 (0.62–1.74)	10.7	0.88 (0.51–1.49)	
Maternal first-degree family history												
Diabetes												
No	390	32.3	1	0.88	6.4	1	0.87	7.7	1.00	17.2	1.00	0.02
Yes	343	31.8	0.98 (0.72–1.33)		6.1	0.95 (0.52–1.73)		14.0	1.91 (1.18–3.11)	14.6	0.89 (0.60–1.34)	
Hypertension												
No	447	30.9	1	0.39	6.0	1	0.74	10.1	1.00	18.3	1.00	0.09
Yes	286	33.9	1.15 (0.84–1.58)		6.6	1.11 (0.60–2.03)		11.5	1.08 (0.67–1.74)	12.2	0.63 (0.41–0.97)	

Table 3—Continued

	n	Primary outcome %	OR (95% CI)	P	Preeclampsia %	OR (95% CI)	P	Customized SGA and LGA SGA (%)	OR (95% CI)*	LGA (%)	OR (95% CI)*	
Glycemia measures												
At baseline (venous plasma)												
75-g OGTT result at diagnosis												
Fasting tertile 1	208	29.8	1.00	0.39	3.4	1.00	0.06	12.5	1.00	9.6	1.00	<0.001
Fasting tertile 2	218	32.6	1.14 (0.75–1.72)		6.4	1.97 (0.78–4.98)		11.5	0.94 (0.52–1.69)	12.4	1.32 (0.71–2.44)	
Fasting tertile 3	228	36.0	1.32 (0.89–1.98)		9.2	2.91 (1.21–7.00)		9.7	0.91 (0.49–1.67)	24.1	2.95 (1.69–5.15)	
2-h tertile 1	206	30.1	1.00	0.09	4.4	1.00	0.19	7.3	1.00	15.5	1.00	0.10
2-h tertile 2	213	28.6	0.93 (0.61–1.42)		5.6	1.31 (0.54–3.17)		12.7	1.81 (0.93–3.53)	13.2	0.88 (0.51–1.53)	
2-h tertile 2	222	37.8	1.41 (0.95–2.12)		8.6	2.05 (0.91–4.64)		13.5	2.12 (1.10–4.10)	18.9	1.39 (0.83–2.32)	
Recruitment A1C												
Tertile 1	223	31.8	1.00	0.73	4.5	1.00	0.04	9.9	1.00	8.1	1.00	0.004
Tertile 2	227	28.6	0.86 (0.57–1.29)		4.0	0.88 (0.35–2.21)		11.5	1.32 (0.72–2.42)	16.3	2.29 (1.26–4.19)	
Tertile 2	214	31.3	0.98 (0.65–1.46)		9.4	2.20 (1.00–4.81)		9.8	1.19 (0.63–2.25)	21.5	3.18 (1.77–5.72)	
During treatment (capillary glucose)												
Fasting means												
Tertile 1	240	22.9	1.00	0.001	4.2	1.00	0.03	13.8	1.00	12.1	1.00	<0.001
Tertile 2	246	32.5	1.62 (1.08–2.42)		4.9	1.18 (0.50–2.78)		11.4	0.80 (0.46–1.37)	11.4	0.91 (0.52–1.58)	
Tertile 3	240	39.6	2.20 (1.48–3.28)		9.6	2.44 (1.13–5.24)		6.7	0.52 (0.28–0.99)	24.6	2.20 (1.34–3.59)	
Postprandial mean glucose												
Tertile 1	238	25.6	1.00	0.002	3.4	1.00	0.002	11.8	1.00	10.1	1.00	<0.001
Tertile 2	248	29.4	1.21 (0.81–1.80)		4.4	1.33 (0.53–3.38)		10.5	0.91 (0.51–1.61)	12.9	1.31 (0.74–2.30)	
Tertile 3	238	40.3	1.96 (1.33–2.90)		10.9	3.53 (1.56–7.96)		9.7	0.98 (0.54–1.77)	24.8	2.93 (1.74–4.93)	
Overall mean glucose (fasting + postprandial)/2												
Tertile 1	239	23.0	1.00	<0.001	3.4	1.00	0.01	13.8	1.00	10.5	1.00	<0.001
Tertile 2	248	31.1	1.51 (1.01–2.26)		5.2	1.60 (0.65–3.93)		9.7	0.69 (0.39–1.21)	13.3	1.25 (0.72–2.19)	
Tertile 3	237	41.4	2.36 (1.59–3.51)		10.1	3.25 (1.43–7.40)		8.4	0.69 (0.38–1.24)	24.1	2.60 (1.54–4.32)	

Data are % or ORs (95% CI). *BMI adjusted for ethnicity. Normal: Polynesian 20–25 kg/m², European 20–24 kg/m², Indo-Asian/other 18–23 kg/m², overweight: Polynesian ≥26–32 kg/m², European ≥25–30 kg/m², Indo-Asian/other >23–27.5 kg/m², obese: Polynesian >32 kg/m², European >30 kg/m², Indo-Asian/other >27.5 kg/m².

Table 4—*Multiple logistic regression model 2: significant factors relating to outcomes*

	Adjusted OR (95% CI)			*P*
Primary outcome composite				
Fasting capillary glucose on treatment				
Tertile 1	1.00			<0.001
Tertile 2	1.75 (1.17–2.63)			
Tertile 3	2.66 (1.76–4.01)			
Nulliparity				
No	1.00			<0.001
Yes	1.85 (1.30–2.65)			
Previous baby >4,000 g				
No	1.00			0.001
Yes	0.58 (0.37–0.90)			
Preeclampsia				
Postprandial capillary glucose on treatment				
Tertile 1	1.00			0.016
Tertile 2	1.38 (0.53–3.49)			
Tertile 3	3.14 (1.31–7.32)			
BMI category				
Normal	1.00			0.036
Overweight	8.48 (1.09–66.22)			
Obese	4.31 (0.55–33.50)			
Weight gain (kg) from early pregnancy to recruitment	1.06 (1.00–1.11)			0.034
Ethnicity category				
European/Caucasian/mixed	1.00			0.041
Polynesian	2.40 (1.12–5.12)			
Asian/other	0.86 (0.35–2.11)			
Chronic hypertension				
No	1.00			0.034
Yes	2.69 (1.08–6.73)			
Previous gestational hypertension				
No	1.00			0.008
Yes	3.26 (1.26–8.40)			
Nulliparity	2.74 (1.32–5.70)			
SGA or LGA	SGA infants		LGA infants	
Postprandial capillary glucose on treatment				
Tertile 1	1.00		1.00	0.001
Tertile 2	0.89 (0.50–1.58)		1.30 (0.73–2.33)	
Tertile 3	0.98 (0.54–1.78)		2.82 (1.65–4.84)	
Previous baby >4,000 g				
No	1.00		1.00	<0.001
Yes	0.60 (0.28–1.28)		3.00 (1.84–4.89)	
Nulliparity	1.20 (0.71–2.04)		0.84 (0.48–1.45)	
Weight gain (kg) from early pregnancy to recruitment	0.94 (0.90–0.99)		1.05 (1.02–1.09)	<0.001
Maternal first-degree relative: diabetes				
No	1.00		1.00	0.01
Yes	2.04 (1.24–3.34)		0.84 (0.54–1.28)	

Data are adjusted ORs (95% CI). BMI range was included in the model to determine whether there was any effect of BMI $\geq$30 kg/m^2. (Customized birth weights already adjust for maternal BMI between 20 and 30 kg/m^2.)

outcome composite, preeclampsia or LGA/SGA infants.

The first multivariable analysis model included baseline glycemia measures to examine whether they related to the chosen outcome measures (model 1). After backward elimination, none of the baseline glycemia measures predicted the primary outcome or preeclampsia, but treatment capillary glucose was strongly related. None of the glucose measures predicted SGA infants. For LGA infants, A1C at recruitment was the only predictive glycemia measure (*P* = 0.003). Compared with the lowest A1C tertile, the

second tertile had an odds ratio (OR) for LGA infants of 2.64 (95% CI 1.33–5.24) and the third tertile had an OR for LGA infants of 4.0 (2.03–7.87).

The results of the second multivariable analysis model (excluding baseline glycemia measures and thus including larger numbers) are summarized in Table 4. Variables that were eliminated for all outcomes are not shown. In this analysis, fasting capillary glucose on treatment was associated with the primary outcome composite, and postprandial capillary glucose was related to LGA infants and preeclampsia. Overweight women were more likely to develop preeclampsia than normal-weight women, but the rate of preeclampsia in obese women was not increased. Numbers of women taking aspirin (n = 45) were too small to determine whether this was a confounding factor. Polynesian ethnicity, chronic hypertension, and previous gestational hypertension remained factors for preeclampsia. Having a previous baby weighing >4,000 g reduced the risk of neonatal complications but increased the risk of LGA infants. Weight gain from early pregnancy to recruitment increased the risk of preeclampsia and LGA infants.

CONCLUSIONS — The key finding from this study is that capillary glucose values during treatment for GDM with metformin and/or insulin related strongly and independently to the primary outcome composite of neonatal outcomes, to maternal preeclampsia, and to frequency of LGA infants. These data are novel in that the outcomes examined seem to be sensitive to different levels of glycemia: rates of neonatal hypoglycemia increased between the lowest and middle tertiles of glycemia control, whereas risk of LGA infants and maternal preeclampsia increased between the middle and highest tertiles. These differential effects may be important to consider when one is determining treatment goals and which outcomes to report in assessing treatment of GDM.

The diagnostic OGTT values were not predictive of outcomes, but A1C at recruitment was predictive of LGA infants. It may be that intervention in the trial was too late to modify this outcome. The fetal ultrasound measurements at recruitment and at 37 weeks of gestation have not yet been analyzed to see whether growth velocity was modified differentially according to glycemic control, as others have shown (3).

During treatment, fasting capillary glucose predicted neonatal complications, whereas postprandial capillary glucose was related to risks of preeclampsia and LGA infants. It is therefore important to focus on both fasting and postprandial glucose control to optimize outcomes. The relationship between postprandial glucose levels and complications may be relevant for obese women without GDM, who have higher postprandial glucose levels and increased rates of preeclampsia and LGA infants compared with lean women (12). In addition, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated that maternal glycemia, as measured by a 75-g OGTT at 28 weeks of gestation, is an important risk factor for preeclampsia and LGA infants at values below those used currently to diagnose GDM (13). A further study has shown that fluctuating glucose levels have a stronger effect on endothelial function (important in the pathogenesis of preeclampsia [14]) than sustained hyperglycemia (15). From these observations, it can be speculated that reducing postprandial glucose fluctuations in obese women could reduce rates of preeclampsia and/or LGA infants.

There was no independent effect of obesity on the primary outcome composite, preeclampsia or LGA infants, consistent with previous findings in women treated with insulin (7). It may be that pharmacotherapy more strongly modifies fetal nutrient supply than dietary intervention alone, overriding the effects of obesity per se.

There was no increase in SGA infants in the lowest glucose tertile, but mean glucose values were above the threshold previously shown to increase risk of SGA infants (9). Customized centiles were used because, particularly in heterogeneous populations, they perform better than does a population centile for identifying SGA infants, both in the general obstetric population and in women with type 2 diabetes (11,16). It is recognized that these calculators require further development in relation to the adjustment for ethnicity and maternal BMI (16).

The rate of SGA infants was increased in women with a first-degree relative with diabetes. The reason for this may relate to genetic associations between low birth weight and type 2 diabetes (17).

There were no differences seen between metformin and insulin treatment groups at different levels of glucose control. This finding suggests that, if met-

formin is used, supplemental insulin should be used readily if glucose targets are not achieved.

These data do not provide definitive answers regarding optimal glucose targets. However, women with mean posttreatment fasting capillary glucose <4.9 mmol/l had significantly better outcomes than women with posttreatment fasting capillary glucose between 4.9 and ≥5.3 mmol/l. At 2 h postprandial, mean capillary glucose ≤6.4 mmol/l was associated with improved outcomes, and a further, but small, improvement was seen with mean postprandial capillary glucose <5.9 mmol/l. In an earlier study, women in a "well-controlled" group had a mean fasting capillary glucose of 4.7 mmol/l and either a mean 1-h capillary glucose of 6.5 mmol/l or a mean 2-h capillary glucose of 5.7 mmol/l, whereas a "less well-controlled" group had a mean fasting capillary glucose of 5.3 mmol/l and either a mean 1-h capillary glucose of 7.2 mmol/l or a mean 2-h capillary glucose of 6.8 mmol/l (6). The glucose means in the well-controlled group were very similar to the means seen in women in the lowest tertile in the current study. These data suggest that clinicians should aim for lower targets than currently recommended.

In summary, these data demonstrate that glucose control in women with GDM is strongly related to pregnancy outcomes. Targets for fasting and postprandial capillary glucose may need to be lower than current guidelines recommend.

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